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# FREQUENCY OF LEFT ATRIAL ENLARGEMENT ACCORDING TO DIFFERENT MODES OF INDEXING IN OVERWEIGHT AND OBESE INDIVIDUALS

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## ABSTRACT

**Background**: Current guidelines recommend indexing left atrial volume (LAV) by body surface area (BSA). However, in overweight and obese individuals this may result in the underestimation of left atrial enlargement (LAE). The aim of our study was to assess whether alternative LAV indexing to height and/or height-squared better identifies individuals with LAE among those who are overweight and/or obese.

**Methods**: LAV was indexed to BSA (LAVI), height (LAVh), and height-squared (LAVh2) in 127 individuals with a mean age of 45.7 years and a mean body mass index (BMI) of 34.9 kg/m2 who underwent outpatient echocardiography at the University clinic of cardiology in Skopje.

**Results**: LAVI, LAVh, and LAVh2 showed a progressive increase of respective values with the extent of BMI showing the most enlarged LA size in individuals with Class III obesity. There was a progressive significant increase in the prevalence of LAEh and LAEh2 in obese groups with the highest prevalence among those with class III obesity (p=0.002, p=0.002, respectively), on the contrary of LAEBSA where we could not find any significance in its distribution among obese classes. The greatest degree of reclassification occurred when indexing for height-squared, having relatively less reclassification when indexing for height (p=0.0001). The degree of reclassification varied depending on BMI with the greatest impact among the Class III obese patients, where as many as 76.5% and 88.2% of individuals were reclassified according to height or height-squared, respectively.

**Conclusions**: The use of height, and especially height-squared, in comparison to BSA-based indexing methods are more successful in identifying the LAE prevalence in each class of obesity. Using allometric indexation leads to the significant reclassification of LA size from normal to dilated, especially in women and those with severe obesity, thereby providing an opportunity to identify more individuals at increased risk of adverse events.

**Keywords**: left atrial enlargement, alternative method of indexing, obesity

## INTRODUCTION

Left atrial enlargement (LAE) is usually a consequence of pressure and/or volume overload of atrial, ventricular, or valvular origin as well as in body size [1–3]. Thus, LAE is commonly found in obese individuals [4–6]. Transthoracic echocardiography is the most widely used method available to identify LAE, done by measuring left atrial volume (LAV) as the preferred method over left atrial diameter, according to the current guidelines of professional societies [7, 8]. Furthermore, their recommendation states that assessment of LAV should be done via indexing it to BSA as it performs better than the left atrial (LA) dimension in predicting adverse cardiovascular events [9]. However, in overweight and obese individuals, indexing LAV for BSA may underestimate the presence and degree of LAE [8, 10, 11] which is why recent hypertension guidelines [12] and data of various studies have suggested height-based indexing of LAV [5, 10–13].

Considering the current levels of obesity in the world and the potential of LAE for adverse cardiovascular (CV) outcomes, we investigated the frequency of LAE using various methods of indexing across the range of BMI categories

## METHODS

*Study population*

127 otherwise healthy individuals (45.7 ± 10.2 y; 61.4% women) with a BMI of 34.90 ± 4.94 kg/m2 underwent outpatient echocardiography at the University Clinic of Cardiology in Skopje. Demographic data, risk factors, and clinical conditions were obtained through detailed history-taking and physical examination. Patients with poor sonographic signal, acute medical illness, ejection fraction < 50%, a history of coronary artery disease, acquired valve and/or congenital heart disease with rhythm and/or conduction abnormalities were excluded from the study. Using BMI, individuals were defined as overweight (BMI ≥25 and <30 kg/m2), obese in class I (BMI ≥30 and <35 kg/m2), class II (BMI ≥35 and <40 kg/m2) and class III severely obese (BMI ≥40 kg/m2). Written informed consent was obtained from all study participants and the Institutional Ethical and Research Board approved the study.

*Echocardiography*

Transthoracic echocardiography using commercially available echocardiographs (GE, Vivid 7) was performed by experienced operators following current guidelines [7] and a standardized protocol. To reduce interobserver variability, all tracings were analyzed by a single cardiologist. The maximal value for LAV was estimated from the left atrial (LA) area in 4-chamber and 2-chamber views and from the shortest of the two LA long axes measured in the apical 2- and 4-chamber views by the area-length technique (ellipsoid model). LAV was then indexed to BSA, height, and height-squared. LAE was defined as follows: 1. > 34 ml/m2 LAV indexed to BSA (LAVI) according to the current ASA/EACVI guidelines [5]; 2. male >35.7 mL/m and female >33.7 mL/m LAV indexed to height (LAVh) according to published reference values [5, 11]; and 3. >18.5 ml/m2 in males and >16.5 ml/m2 in females, LAV indexed to height-squared (LAVh2) according to ESC/ESH hypertension guidelines [12] and published reference values [11]. Significant reclassification was considered to have occurred in individuals whose LAV was nondilated when indexed for BSA and dilated when indexed for height, or height-squared.

*Statistical analysis*

Categorical parameters were summarized as percentages and continuous parameters as a mean ± standard deviation. The difference between groups was tested using Pearson's Chi-square test for categorical variables and Wilcoxon paired and Mann-Whitney nonparametric tests or analysis of variance (ANOVA) for continuous variables. We performed a post hoc analysis for multiple comparisons using the Bonferroni test. Assessment of correlation was done using Pearson's correlation analysis. All data analysis was performed using SPSS version 25.0 (IBM SPSS, Inc., Chicago, Illinois, USA), and p ≤ 0.05 was considered as statistically significant.

## RESULTS

*Baseline characteristics*

The baseline characteristics of the study cohort are listed in Table 1. 61.4% of the cohort was female and the average age was 45.7 years. Individuals with obesity in Class II and Class III were younger than those who were overweight (p=0.023), thereby showing a significant negative correlation with BMI (r=-0.244, p=0.006). The mean BMI was 34.90 kg/m2. Out of all participants 18(14.2%) were overweight, 51 (40.2%) were obese in Class I, 41 (32.3%) were obese in Class II and 17 (13.4%) in class III. The most frequent mean duration of obesity was 5-10 years without any significant difference among the groups. Baseline CV risk factors showed that hypertension was present in 50%, dyslipidemia in 57.1%, and diabetes in 20.0% of individuals without significant difference among the groups.

*Baseline echocardiographic characteristics*

Echocardiographic characteristics are presented in Table 1. The mean left ventricular (LV) ejection fraction was 66.8 %. The mean LA dimension was 39.7 mm and LAV was 58.3 mL showing a significant increase in size in Class II and/or Class III obese individuals (p=0.008, p=0.003, respectively). Multiple comparisons showed that the LA dimension in individuals with Class II and Class III obesity was significantly more increased than in overweight ones while maximal LAV was significantly increased in Class III obese in comparison to overweight individuals. Indexing LAV for BSA (LAVI), for height (LAVh), and for height-squared (LAVh2) showed a progressive increase of respective values with the extent of BMI, showing the most enlarged LA size in individuals with Class III obesity. However, there was a significant difference among the groups of obesity only for LAVh (p=0.002) and LAVh2 (p=0.002), showing a significant difference between Class III obesity vs. those who were overweight and/or were classified with Class I obesity. Analysis of correlations showed a significant positive association of BMI with LA size (r=0.300, p=0.001), LAV (r=0.299, p=0.001), LAVh (r=0.323, p=0.0001) and LAVh2 (r=0.331, p=0.0001), but this association was missing for LAVI.

The LAE prevalence among the obese classes according to the recommended definitions (5, 11, 12) is presented in Table 2. LAE in individuals with indexed LAV for BSA (LAEBSA) was observed in 20/15.7%, among those with LAV indexed by height (LAEh) in 56/44.1%, and among those with LAV indexed by height-squared (LAEh2) in 89/70.1% individuals. There was a progressive significant increase in the prevalence of LAE in obese groups with the highest prevalence among those with class III obesity. On the contrary, when we assessed LAEBSA using LAV indexed to BSA, we could not find any significance in its distribution among the obese classes. Multiple comparisons showed that the prevalence of LAEh in class III was significantly higher in comparison to all other groups while the prevalence of LAEh2 was significantly higher in class III in comparison to overweight. The differences between LAV alternative indexing among each group presented in Table 3 shows that indexing LAV to BSA caused LAE prevalence and that indexing for height and/or height-squared to be

**Table 1.** *Baseline clinical characteristic and echocardiographic parameters.*

| | Whole cohort (n=127) | Overweight (n=18) | Class I obesity (n=51) | Class II obesity (n=41) | Class III obesity (n=17) | P value |
|---|---|---|---|---|---|---|
| Age at echo (y) | 45.7 ± 10.2 | 50.6 ± 10.3 | 47.0 ± 10.3 | 42.8 ± 9.6 | 43.1 8.6 | 0.023 |
| Female (n/%) | 78/61.4% | 14/77.8 | 29/56.9 | 24/58.5 | 11/64.7 | 0.440 |
| BMI (kg/m2) | 34.90 ± 4.94 | 28.31 ± 1.29 | 32.29 ± 1.41 | 37.36 ± 1.98 | 43.77 ± 2.27 | 0.0001 |
| Height (cm) | 170.93 ± 0.10 | 167.50 ± 0.81 | 171.18 ± 0.10 | 172.44 ± 0.09 | 170.18 ± 0.10 | 0.372 |
| Weight (kg) | 102.50 ± 18.83 | 80.61 ± 8.00 | 94.78 ± 11.00 | 111.49 ± 14.22 | 127.12 ± 16.17 | 0.0001 |
| BSA (m2) | 2.13 ± 0.25 | 1.90 ± 0.14 | 2.07 ± 0.18 | 2.23 ± 0.20 | 2.35 ± 0.23 | 0.0001 |
| Risk factors<br>Hypertension (%)<br>Dyslipidemia (%)<br>Diabetes (%) | <br>50.0<br>57.1<br>20.0 | <br>50.0<br>57.1<br>30.8 | <br>51.4<br>69.4<br>18.2 | <br>42.9<br>39.3<br>19.2 | <br>61.5<br>61.5<br>15.4 | <br>0.731<br>0.113<br>0.755 |
| **Echocardiographic characteristics** | | | | | | |
| LA dimension (mm) | 39.7 ± 4.4 | 36.7 ± 4.3 | 39.7 ± 3.6 | 40.6 ± 4.6 | 41.0 ± 4.6 | 0.008 |
| LAV (ml) | 58.36 ± 16.59 | 48.85 ± 12.89 | 56.50 ± 12.88 | 60.85 ± 20.88 | 67.97± 12.43 | 0.003 |
| LAVI (ml/m2) | 27.22 ± 6.58 | 25.53 ± 5.46 | 27.30 ± 5.65 | 27.06 ± 8.34 | 29.17 ± 5.36 | 0.443 |
| LAVh (ml/m) | 34.02 ± 8.88 | 29.01 ± 6.75 | 32.97± 6.86 | 35.08± 11.05 | 39.91 ± 6.94 | 0.002 |
| LAVh2 (ml/m2) | 19.90± 5.02 | 17.26 ± 3.61 | 19.31± 4.08 | 20.29 ± 6.03 | 23.51 ± 4.28 | 0.002 |
| LVEF (%) | 66.8 ± 7.5 | 68.8 ± 6.9 | 66.7 ± 6.9 | 65.7 ± 8.0 | 67.3 ± 9.1 | 0.537 |

BMI = body mass index; BSA = body surface area; h=height; h2=height-squared; LA = left atrial; LAV=left atrial volume; LVEF=left ventricular ejection fraction

**Table 2.** *Prevalence of LAE based on LAV alternative indexing.*

| | Overweight (n=18) | Class I obesity (n=51) | Class II obesity (n=41) | Class III obesity (n=17) | P value |
|---|---|---|---|---|---|
| $LAE_{BSA}$ (n/%) | 2/11.1 | 7/13.7 | 9/22.0 | 2/11.8 | 0.606 |
| $LAE_h$ (n/%) | 3/16.7 | 20/39.2 | 18/43.9 | 15/88.2 | 0.0001 |
| Class III vs overweight (p=0.0001), class I (p=0.001) and class II (p=0.008) | | | | | |
| $LAEh_2$ (n/%) | 10/55.6 | 35/68.6 | 27/65.9 | 17/100 | 0.024 |
| Class III vs overweight (p=0.024) | | | | | |

LAE=left atrial enlargement; $LAE_{BSA}$=left atrial enlargement od LAV indexed by BSA; $LAE_h$= left atrial enlargement indexed by height, $LAE_{h2}$=left atrial enlargement indexed by height-squared; LAV=left atrial volume.

**Table** *3. Differences between LAV alternative indexing among each group.*

| | Overweight (n=18) | Class I obesity (n=51) | Class II obesity (n=41) | Class III obesity (n=17) |
|---|---|---|---|---|
| $LAE_{BSA}$ vs $LAE_h$ | 0.331 | 0.0001 | 0.002 | 0.0001 |
| $LAE_{BSA}$ vs $LAE_{h2}$ | 0.002 | 0.0001 | 0.0001 | 0.0001 |
| $LAE_h$ vs $LAE_{h2}$ | 0.004 | 0.0001 | 0.002 | 0.163 |

LAE=left atrial enlargement; $LAE_{BSA}$=left atrial enlargement od LAV indexed by BSA; $LAE_h$= left atrial enlargement indexed by height, $LAE_{h2}$=left atrial enlargement indexed by height-squared; LAV=left atrial volume.

**Table 4.** *Reclassification of LA size based on alternative indexing.*

| % Reclassified | Height | Height-squared | p value |
|---|---|---|---|
| whole cohort (n/%) | 38/29.9 | 67/52.8 | 0.0001 |
| men | 17/34.7 | 21/42.9 | 0.356 |
| women | 21/26.9 | 46/59.0 | 0.078 |
| Overweight (n/%) | 2/11.1 | 7/38.9 | 0.020 |
| Class I (n/%) | 13/25.5 | 27/52.9 | 0.0001 |
| Class II (n/%) | 10/24.4 | 18/43.9 | 0.003 |
| Class III (n/%) | 13/76.5 | 15/88.2 | 0.163 |
| **p value** | 0.0001* Class III vs all others | 0.009* Class III vs Class II & overweight | |

*significance depending on BMI; LA=left atria.

underestimated and it seemed thus to be more effective for this purpose. Indexing for height and height-squared led to a significant reclassification of LA size from normal to dilated especially in women. Rates of reclassification from normal to dilated by each indexing method are presented in Table 4. The greatest degree of reclassification occurred with indexing for height-squared with relatively less reclassification with indexing for height (p=0.0001). The degree of reclassification varied depending on BMI with the greatest impact in the Class III obese, where as many as 76.5% and 88.2% of individuals were reclassified according to height or height-squared, respectively.

## DISCUSSION

The results of our study have demonstrated that the use of height, and especially height-squared, in comparison to BSA-based indexing methods are more valid means to identify the LAE prevalence in each class of overweight and/or obesity. Indexing for height and height-squared led to the significant reclassification of LA size from normal to dilated. However, analysis of our cohort showed that the greatest degree of reclassification occurred with indexing for height-squared which suggests that BSA-based indexing for LA dilation is a poor discriminator in the obese and, therefore, diagnosing LA dilation using BSA-based indexing is suboptimal, eventually leading to misidentification of individuals at increased risk. Having in mind that LAE has a potentially important clinical significance concerning its ability to predict mortality and CV events [9, 11, 14] along with the increased prevalence of obesity around the world, it has become of considerable importance to use the correct method in indexing the LA size.

The use of alternative methods of indexing LA size in obese individuals has been a subject of several published studies [5, 10–16] that have shown that when LA size was indexed based on methods that were not weight dependent, a higher prevalence of LAE was noted. Yao et al. [15] examined 266 overweight and obese individuals (divided into 3 classes) along with 46 controls with normal BMI for different indexing methods of LA dimension (LAD) and showed that LAD was overcorrected by body weight, BMI, and/or BSA, but indexing LAD to height showed a significant and graded increase across the groups of increased BMI; thus, authors concluded that it should be the preferred method in indexing LAD among the obese. Stritzke et al. [5] evaluated the association of obesity and hypertension with LAE in 1212 individuals and its prognosis over 10 years. They assessed LA size indexed to height and found that the prevalence of LAE was significantly lower when it was assessed using the indexing LA size to BSA, especially in obese individuals, leading to the conclusion that the indexing of LA volume by body height enhanced the ability to detect LAE related to obesity. Airale et al. (16) tested the difference in LAE prevalence in 441 essential hypertensive patients by using two different diagnostic criteria: LA indexed to BSA (LAEBSA) and indexed to height-squared (LAEh2). In line with our study, they found that the prevalence of LAE was twice as high when using LAEh2 indexation rather than BSA (50.6% vs. 23.4%, $p < 0.001$). They also found that LAE was significantly more prevalent in female patients than in male when using height-squared. Yejaprakash et al. [13] performed a structured search of medical databases and identified 13 relevant articles discussing alternative methods of LA indexation in echocardiography, of which nine reported allometric indices. Compared with isometric indexation to BSA, allometric indexation (specifically to height) improves the scaling of LA volumes to avoid overcorrection for body size. The European Society of Cardiology (ESC) guidelines on the management of arterial hypertension in adults [12] recommend using LA volume indexed to height-squared to define normal LA size with sex difference (≤18.5 mL/m2 for men; ≤16.5 mL/m2 for women). Furthermore, Badano et al. [17] emphasized in their editorial that in order to make a better difference between normal and abnormal results, the use of allometric equations that take into account body metrics (but no BSA), age, and sex would be more wise approach in the assessment of LAV especially when the possible CV events are into account.

## LIMITATION OF THE STUDY

Although according to ASE [7], the volumetric method in the assessment of LAV is recommended, we have used an alternative and an acceptable area-length method which is standard procedure at our institution. Considering that our primary goal was to compare different methods of indexing and the same method of assessing LAV was used for all indexing techniques, we think the comparison between indexing methods is valid.

The limited number of participants in our study emerges as a constraint, as this study was conducted under limited Covid-induced circumstances.

## CONCLUSION

Indexing LAV to BSA substantially underestimates the prevalence of LAE in individuals with overweight and obesity which is why indexation to height and for height-squared is preferred. Using allometric indexation leads to the significant reclassification of LA size, especially in women and those in Class III obesity which provides an opportunity to identify more individuals at increased risk of adverse events.

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**Резиме**

**ФРЕКВЕНЦИЈА НА ЗГОЛЕМУВАЊЕ НА ЛЕВАТА ПРЕТКОМОРА СПОРЕД РАЗЛИЧНИ НАЧИНИ НА ИНДЕКСИРАЊЕ КАЈ ИНДИВИДУИ СО ПРЕКУМЕРНА ТЕЛЕСНА ТЕЖИНА И ДЕБЕЛИНА**

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**Вовед**: Актуелните водичи препорачуваат индексирање на волуменот на левата преткомора (ЛПВ) со површината на телото (body surface area-BSA). Но, овој вид индексирање може да го потцени левопреткоморното (ЛП) зголемување кај индивидуите со прекумерна тежина и дебелина. Целта на нашата студија беше да процениме дали алтернативното ЛП-индексирање со висината иили квадратот на висина подобро го идентификува ЛП-зголемувањето кај индивидуите со прекумерна телесна тежина и дебелина.

**Методи**: Волуменот на ЛП беше индексиран со BSA (LAVI), со висината (LAVh) и квадратот на висината (LAVh2) кај 127 лица со просечна возраст од 45,7 години и просечен индекс на телесна маса (BMI) од 34,9 kg/m$^2$, кои беа амбулантски ехокардиографски евалуирани на Универзитетската клиника за кардиологија во Скопје.

**Резултати**: Вредостите на LAVI, LAVh и LAVh2 покажаа прогресивно зголемување поврзано со степенот на BMI. Притоа, најголемо зголемување на ЛП имаше кај индивидуите од класа III дебелина.

Кај групите со дебелина имаше значајно прогресивно зголемување на преваленцата на LAEh и LAEh2, со највисока преваленца во класа III дебелина (p = 0,002, p = 0,002, соодветно), што е спротивно од LAVI, за кој не можевме да најдеме никакво значење во неговата дистрибуција во класите дебелина.

Најголем степен рекласификација се случи со индексирањето за висина-квадрат, а релативно помала рекласификација имаше со индексирањето за висината (p = 0,0001). Степенот на рекласификација варираше во зависност од БМИ со најголемо влијание кај класа III дебелина, каде што дури 76,5 % и 88,2 % од индивидуите беа рекласифицирани според висината или квадратот на висината, соодветно.

**Заклучок**: Споредбено со BSA, висината и, особено, квадратот на висината се повалидни методи на индексација на ЛП за идентификација на преваленцата на зголемувањето на ЛП кај индивидуите со дебелина. Алометриската индексација овозможува значајна рекласификација на големината на ЛП, од нормална во проширена, особено кај жените и кај изразената дебелина, и преставува можност да се идентификуваат повеќе лица со зголемен ризик од несакани случувања.

**Клучни зборови**: левопреткоморно зголемување, алтернативен метод на индексирање, дебелина